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The relationship between breast cancer treatment, tumour type and vitamin D level in pre- and postmenopausal women

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Abstract

OBJECTIVE: Vitamin D deficiency has been linked to a higher risk of cancer. There is insufficient data regarding the influence of treatment on vitamin D status. The aim of this study was to compare pre- and post-treatment levels of 25(OH)D in premenopausal and postmenopausal women with breast cancer with a different receptor status (ER-estrogen receptors, PR-progesterone receptors) and in healthy controls.

METHODS: 49 patients with breast cancer (23 premenopausal), and 28 healthy controls matched for age, menopausal status and BMI.

RESULTS: The pre-treatment levels of 25(OH)D in patients with breast cancer were significantly lower in comparison to the control group (19 ng/mL vs. 30 ng/mL, $p<0.001$), the lowest in premenopausal women (18.4 ng/mL). After the treatment period, a significant decrease in 25(OH)D level (mean 15.8 ng/mL) was observed. The pre-treatment level of 25(OH)D was significantly lower in patients with ER (16.1 vs. 23.9 ng/mL, $p=0.02$) and with PR (15 vs. 24.4 ng/mL, $p=0.003$). The mean pre- and post-treatment levels of 25(OH)D were lower in patients with Ki67 <21% (16.7 vs. 20.1 ng/mL, $p=0.15$; 12.5 vs. 18.1 ng/mL, $p=0.02$ respectively).

ORIGINAL ARTICLE

CONCLUSIONS: 25(OH)D level is lower in patients with breast cancer in comparison to healthy women, regardless of their menopausal status. The lowest levels are found in patients with ER and PR positive tumours. While a significant decrease in 25(OH)D level during the course of therapy is observed, the supplementation of vitamin D should be considered.

INTRODUCTION

Vitamin D is a group of steroid-like molecules which are similar to classical steroid hormones. The main biological role of vitamin D is the maintenance of calcium homeostasis by increasing intestinal absorption of calcium and decreasing its excretion by the kidneys (Leyssens *et al.* 2013; Feldman *et al.* 2014; Christakos *et al.* 2016). Nevertheless, vitamin D has also been implicated in several other biological processes such as the induction of apoptosis, modulating the immune system, inhibiting inflammation, blocking cell proliferation and promoting cell differentiation (Leyssens *et al.* 2013; Feldman *et al.* 2014; Christakos *et al.* 2016). Because of its pleiotropic actions, vitamin D has been widely investigated in several different diseases, especially in cancer (Feldman *et al.* 2014). Previously published studies suggest that higher levels of 25-hydroxyvitamin D [25(OH) D] are variably associated with lower breast cancer risk, especially in postmenopausal women (Bauer *et al.* 2013; Wang *et al.* 2013). The data regarding the role of 25(OH)D and breast cancer risk in younger age groups is conflicting (Abbas et al.,2008). Also the association between circulating vitamin D levels and breast cancer risk with regard to different subtypes based on clinical markers such as estrogen receptors (ER) and progesterone receptors (PR) remains unclear to date (Yao S *et al.* 2011). The majority of the studies were focused on the analysis of the relationship between pre-treatment levels of 25(OH)D and cancer development. There is no data regarding the influence of treatment on vitamin D status.

The aim of the present study was to compare pre-treatment and post-treatment levels of 25(OH)D in premenopausal and postmenopausal women with breast cancer and in healthy controls. The authors also aimed to analyse differential effects of 25(OH)D level by receptor status of the tumour type, estrogen receptor (ER) status, and progesterone receptor (PR) status.

Tab. 1. Treatment methods in the investigated group.

	Treatment	No.
chemotherapy	FEC	15
	AC	9
	AC /PTX	14
	AT	
RTX	radiotherapy	37
hormone therapy	tamoxifen	18
	aromatase inhibitor	10
	GnRH analogue	3
immunotherapy	trastuzumab	16

FEC –5 fluorouracyl , epirubicin, cyclofosfamid
AC – doxorubicin , cyclofosfamid
AC/PTX – doxorubicin , cyclofosfamid /PTX- paclitaxel weekly
AT – doxorubicin , taxotere
RTX – radiotherapy

MATERIAL AND METHODS

The study included 49 patients with breast cancer (23 premenopausal), and 28 healthy controls matched for age, menopausal status and BMI (25.2 kg/m^2 vs. 25.9 kg/m^2, p=0.08).

All the patients had undergone surgery, and subsequently received standard adjuvant chemotherapy and, in selected cases, also radiotherapy. Additionally, patients with positive ER received hormone therapy after completing chemotherapy, and patients with positive human epidermal growth factor receptor 2 (HER2) expression received adjuvant immunotherapy (trastuzumab). Details are presented in Table 1.

Total 25(OH)D was assessed in blood samples using the immunochemistry method (ECLIA) with a Cobas e411 analyser (Roche Diagnostics GmbH, Mannheim, Germany).

Statistics

Statistical significance of differences between two independent groups was assessed using the Mann-Whitney test or Student's t- test.

Ethics

The investigation was conducted according to the principles expressed in the Declaration of Helsinki. The study has been approved by the Jagiellonian University Bioethical Committee.

RESULTS

The level of pre-treatment 25(OH)D in patients with breast cancer was significantly lower in comparison to the control group (19 ng/mL vs. 30 ng/mL, p<0.001). The lowest level was observed in premenopausal women (18.4 ng/mL vs. 19.4 ng/mL in the postmenopausal group), however, the difference was not significant. After the treatment, the period control assessment revealed a significant decrease in 25(OH)D level (mean 15.8 ng/mL) in the whole group, both in premenopausal and postmenopausal women (16.6 and 15 ng/mL respectively).

The pre-treatment level of 25(OH)D was significantly lower in patients with the presence of ER in the tumour (16.1 vs. 23.9 ng/mL, p=0.02). The difference

was observed also after completing the treatment. However, it was no longer significant (15 ng/mL vs. 17.1 ng/mL, p=0.2).

Even greater differences were observed regarding the expression of PR. The level of 25(OH)D was significantly lower in patients with the presence of PR in the tumour before the treatment (15 vs. 24.4 ng/mL, p=0.003), and after completing the treatment (13 ng/mL vs. 19.5 ng/mL, p=0.02).

The mean pre-treatment and post-treatment levels of 25(OH)D were lower in patients with Ki67 <21% (16.7 vs. 20.1 ng/mL, p=0.15; 12.5 vs. 18.1 ng/mL, p=0.02 respectively).

DISCUSSION

There has been long-standing interest in the potential role of vitamin D in the development of breast cancer, its recurrence and mortality, considering that, as a steroid-like molecule, it can modulate gene expression through binding to its specific nuclear receptor. The most important source of vitamin D is the conversion of dehydrocholesterol to cholecalciferol in the skin. In order to become a biologically active form of vitamin D, cholecalciferol undergoes two hydroxylation reactions to 25(OH)D in the liver and subsequently to 1.25(OH)2D in the kidneys. 1.25(OH)2D, also known as calcitriol, is a biologically active form of vitamin D. (*Narvaez et al. 2014*). Despite that calcitriol is an active form of vitamin D, its concentration level is not investigated routinely due to its very short half-life. It is better to measure the serum concentration of 25(OH)D, which has a relatively longer half-life (approximately 15 days). A large number of studies have related blood levels of 25(OH)D to cancer incidence and survival (Feldman *et al.* 2014; Albanes *et al.* 2015).

It has been suggested that vitamin D and its metabolites can reduce the incidence of many types of cancer by inhibiting tumour angiogenesis, stimulating mutual adherence of cells, and enhancing intercellular communication through gap junctions, thereby strengthening the inhibition of proliferation which results from tight physical contact with adjacent cells within a tissue (contact inhibition). Vitamin D can inhibit the mitosis of breast epithelial cells. Pulsatile release of ionized calcium from intracellular stores, including the endoplasmic reticulum, induces terminal differentiation and apoptosis (Duffy *et al.* 2017).

Low blood levels of 25(OH)D have been associated with an increased risk of developing breast cancer and poor outcome following the diagnosis of this disease (Maalmi *et al.* 2014; Kim and Je, 2014; Mohr *et al.* 2014; Park *et al.* 2015). Other recently performed meta-analyses, as well as large observational studies, have confirmed this inverse association between low levels of 25(OH)D and both increased risk and poor outcome from breast cancer (Kim and Je, 2014; Mohret *et al.* 2014; Park *et al.* 2015). The majority of the published data points to a close relationship between low 25(OH)D3 and breast cancer risk in postmenopausal women, while disproving the existence of such a relationship in younger population (Garland *et al.* 2008; Kim *et al.* 2014). Our data indicates that a decreased level of 25(OH)D has been observed in patients with breast cancer regardless of their menopausal status.

However, while many studies have focused on the contribution of vitamin D deficiency to the breast cancer development, only a few included an analysis regarding different subtypes based on clinical markers such as ER and PR. Since breast cancer is a heterogenous group of the disease, clinical markers including ER and PR have long been used to classify breast cancer subtypes associated with differential prognosis and response to cancer therapy. Recently published studies showed that among premenopausal women with invasive breast cancer, those who had lower serum 25OHD concentrations were at risk of development of high grade or ER negative cancer (Yao S *et al.* 2011, Abbas et al.,2008). There is no conclusive data pertaining to postmenopausal women. The results of the present study show that low levels of 25(OH)D can predispose to the development of ER and PR positive breast cancer in the premenopausal and postmenopausal women.

Interestingly, the present study provided a novel insight in the form of a significant decrease in 25(OH)D level during the course of therapy. As the positive role of vitamin D in the risk reduction of recurrence and a better overall prognosis have been described, it might be important to control the 25(OH)D level during the therapy and supplement vitamin D.

CONCLUSIONS

25(OH)D level is lower in patients with breast cancer in comparison to healthy women, irrespective of their menopausal status. The lowest levels are found in patients with ER and PR positive tumours. While a significant decrease in 25(OH)D level during the course of the therapy is observed, the supplementation of vitamin D should be considered.

Conflict of interest

The authors declare no competing interests.

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